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Synthesis of selenium-containing alkyl products.

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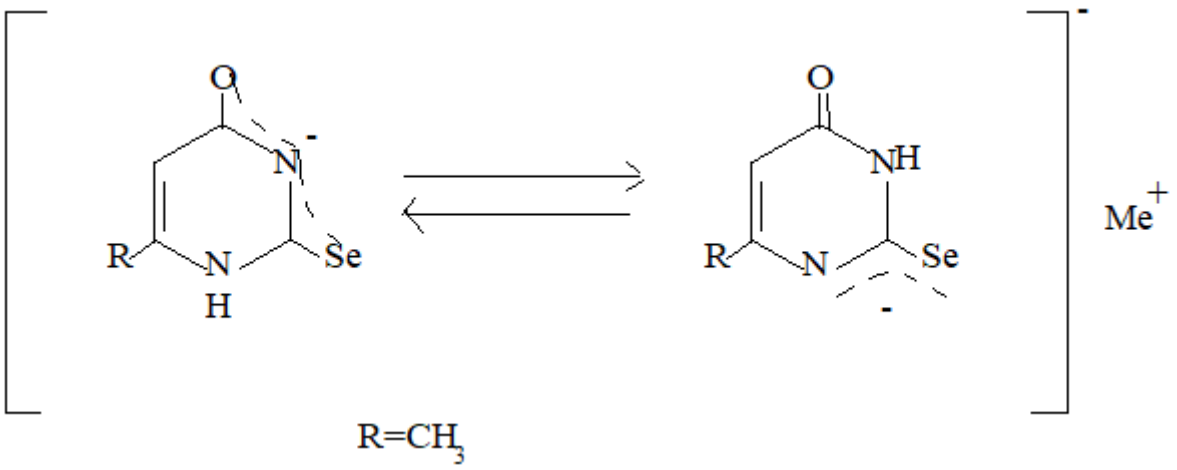
Abstract: We have studied the alkylation reactions of 2-selenoxo-6-methylpyrimidin-4-one with higher C4 -C9 alkyl halides. It was shown that the reaction proceeds mainly by the N3 and O4 reaction centers. We proved this by physicochemical method of analysis (IR, PMR, Mass)

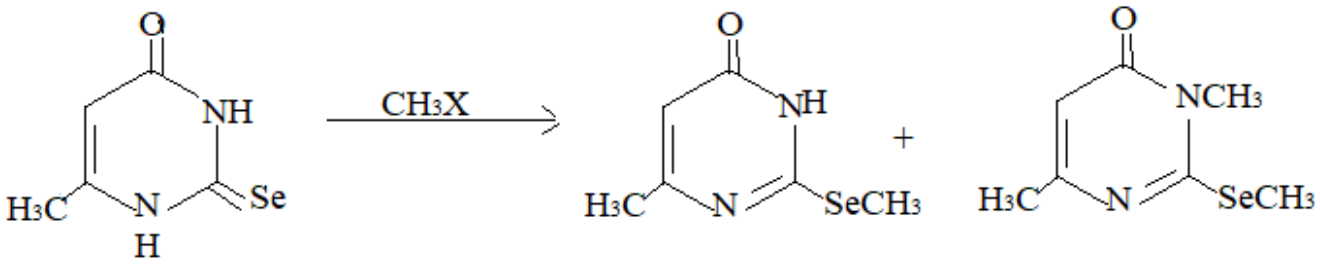
Keywords: alkyl, selenoxo, pyrimidinone, alkyl product, solvent, spectrum, density, electron, nucleophile, heteroatom.

There are four potential reaction centers in the molecule of 2-selenoxo-pyrimidinones-4 as in the case of 2-oxo, thioxo-pyrimidinones-4. The negative charge in their anions is localized at the oxygen atom, although it is delocalized along the system of conjugated bonds or at the N1 atom in the second fragment, when the system is involved in the delocalization of the negative charge [1]



The electron density distribution has a strong influence on the basicity of the reaction centers and determines the direction of the reaction. In this respect, the nature of the heteroatom in the 2nd position of pyrimidinone-4, i.e., in this case the oxygen, sulfur, and selenium atom, plays a significant role.

Methylation of 6-methyl-2-selenoxopyrimidinone-4 with methyl iodide and methyltosylate in alcohol, dioxane, acetonitrile, DFA, DMSO both at room temperature and under heating results in the formation of 6-methyl-2-methylselenoxopyrimidinone-4 exclusively except for its alkylation with methyl iodide in DFA under heating. The formation of the latter is the result of alkylation of the originally formed 6-methyl-2-methylselenopyrimidinone-4 with another methyl iodide molecule.



Their ratio was 1.7:1. The formation of dimethylation products often occurs during alkylation of 2-substituted pyrimidinones-4, especially in the case of 2-thioxopyrimidinones-4.

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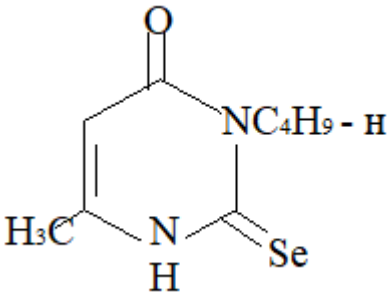
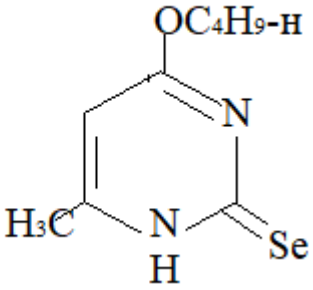
To study the alkylation reaction of 2-selenoxo-6-methylpyrimidinone-4 and to compare the obtained data with its oxo- and thioxoanalogues we performed alkylation of it with C4 -C9 alkyl halides in different solvents [2].

Alkylation with n-butyl bromide in absolute alcohol gives a mixture of products by nitrogen atom at N-3 and oxygen. The amount of 2-selenoxo-4-n-butyloxy-6-methylpyrimidine leaves 6-8%. In the PMR spectrum of the reaction mixture there are methylene group proton signals at N-3 at 3.15 m.p.a. (triplet, CH2-N) and the methyleneoxy group of the O4- alkylation product at 4.15 m.p.a. (triplet, O- CH2). The end methyl group protons appear at 0.70 m.p.a., the methylene protons at 1.25 and 1.62 m.p.a. (multiplet, 2- CH2), methyl group protons at C-6 at 2.06 m.p.a. (singlet), and H-5 at 6.15 m.d. (singlet).





The assignment of these products to the N-3 and O-4 isomers was based on the comparison of the characteristics of their PMR spectra with those of 2-selenoxo-3,6-dimethyl-2-methylseleno-6-methylpyrimidinones-4. The PMR spectrum of 2-selenoxo-3,6-dimethylpyrimidinone-4 is characterized by the presence of three resonance lines at: 1.93 (C6-CH3, 3H, singlet), 3.45 (N-CH3, 3H, singlet), and 5.87 m.d. (H-5, 1H, singlet). The PMR spectrum of 2-methylthio-6-methylpyrimidinone-4 consists of three singlet signals at 2.07 m.p. (C6-CH3, 3H), 2.42 m.d. (SeCH3, 3H) and 6.12 m.d. (H-5,1H).

The formation of an O4 -methyl product without affecting the S-center, that is, with S- and N3 isomers, was observed upon methylation of 2-thioxo-6-phenylpyridinone-4 with methyltosylate in DMF.

Conducting the reaction in the aprotonic dipolar solvent DMF led to an increase in the N3-center fraction of the product. The same picture was observed in increasing of alkylating agent "hardness" as in our case of alkylation of 2-selenoxo-6-methylpyrimidinone-4 with n-butyl bromide.

Experimental part.

Tesla BS-567A (internal TMC standard, GMDS, δ scale). Rf values were determined on "Silufol" UV-254 plates (Czechoslovakia). Illuminant: iodine vapor.

Solvents (acetonitrile, alcohol (ethyl) DMFA, DMSO) were purified and absolute according to the method [3]

Synthesis of 2-selenoxo-6-methylpyrimidinone-4.

In a 250 mL 4-neck flask equipped with a mechanical stirrer, a reflux condenser with a thermometer and a nitrogen tube 3.16 g selenium (Se) and 52 mL water were placed and stirred in a nitrogen atmosphere for 20 minutes. Then 3.04 (82 mmol) sodium borohydride was added in portions. After adding the full amount of NaBH4, it was stirred for another 20 minutes at room temperature and 1 hour at 40˚C. It was cooled and 3.1 g (20 mmol) of 2-methylthio-6-methylpyrimidinone-4 was added and heated in a boiling water bath for 2 hours. The precipitate (mixture of selenium and 2-methylthio-6-methylpyrimidinone-4) was cooled, filtered (2.4 g), the filtrate was acidified with ice-cold acetic acid to pH=7. The precipitated reddish precipitate was filtered off. The reddish precipitate was recrystallized from (DMFA+Water). Yield: 0.16 g (84%) Mel=235-240˚C.

General methodology for alkylation of 2-selenoxo-6-

methylpyrimidinone-4.

In a 100 ml flask was placed 10 ml of absolute alcohol, 0.28 g (5.0 mmol) of KOH, was stirred until caustic potash was completely dissolved. Then 1.0 g (5.3 mmol) of 2-seleno-6-methylpyrimidinone-4 was added and stirred for 30 minutes at room temperature. After that 5.3 mmol of alkylating agent was added to the reaction mixture and heated in a water bath for 4 hours. It was cooled, extracted with chloroform, dried over anhydrous sodium sulfate. Chloroform was stripped off, the residue was analyzed by PMR spectroscopy.

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Alkylation of 2-selenoxo-6-methylpyrimidinone-4 with excess
n-butyl bromide.

To a solution of 0.30 g (5.3 mmol) KOH in 10 ml of absolute alcohol was added 1.0 g (5.3 mmol) of 2-selenoxo-6-methylpyrimidinone-4, stirred for 30 minutes at room temperature, added 5.0 ml (47 mmol) of n-butyl bromide and heated in a water bath for 4 hours. It was cooled, extracted with chloroform, dried over anhydrous sodium sulfate. The chloroform was distilled off. The precipitate was filtered and recrystallized from DMF+Water mixture. We obtained 20 mg (15%) of 2-n-butylseleno-3-n-butyl-6-methylpyrimidinone-4 with Tpl =82-85˚C.

Mass spectrum m/z (Jotn.%) : 301 (M+; 25), 273 (M+-28; 100), 246 (M+-53; 33), 237(M+-64; 33), 204 (M+-97; 33) , 202 (M+-99; 33), 191 (M+-110; 91), 189 (M+-112; 50), 166 (M+-135; 75), 152 (M+-149; 33), 143 (M+-158; 33), 128 (M+-173; 41), 111 (M+-180; 58), 110 (M+- 191; 83).

Preparation of 2-tret-butylseleno-6-methylpyrimidinone-4.

Similarly to the above described solution with 10 mL of absolute DMF, 0.30 g (5.3 mmol) of caustic potassium, 1.0 g (5.3 mmol) of the starting compound and 0.59 mL (5.2 mmol) of butyl tret-bromide gave 0.05 g (22%) of product with mel.=258-261˚C (ethanol) IR spectrum: 1642 (ν=CO), 1559 (νC=N).

Preparation of 2-nonylseleno-6-methylpyrimidinone-4.

Similarly to the above described from a solution with 10 mL of absolute alcohol, 0.30 g (5.3 mmol) of caustic potassium, 1.0 g (5.3 mmol) of the starting compound and 1 mL (5.0 mmol) of n-iodide nonyl was obtained 0.02 g (16%) of product with Tpl.=75-77˚C (DMFA + Water). IR spectrum: 1677 (ν=CO), 1560 (νC=N).

Conclusion: Some alkylation reactions of 2-selenoxo-6-methylpyrimidin-4-one with higher alkyl halides have been shown in this paper, as well as some physico-chemical parameters of the synthesized alkyl products, which found possible applications in medicine as anticancer drugs.

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